JC14 Rec'd PCT/PTO 30 NOV 2001

FORM PTO-1390
(REV. 9-2001)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY 'S DOCKET NUMBER
14081-1US JA/ld

U S. APPLICATION NO. (If known, see 37 CFR 1.5
09/980163

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/CA00/00998	August 28, 2000	September 3, 1999

TITLE OF INVENTION
METHOD OF OPTIMIZING PARAMETER VALUES IN A PROC ESS OF PRODUCING A PRODUCT

APPLICANT(S) FOR DO/EO/US
M'Hammed MOUNTASSIR

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☑ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☑ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☑ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☑ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☑ is attached hereto (required only if not communicated by the International Bureau).
   b. ☐ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☑ Amendments to the claims of the International Aplication under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☑ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☑ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English lanugage translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☑ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☑ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☑ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☑ Other items or information: Petition to Make Special under 37 CFR 1.102 and MPEP 708.02 (VIII) with Annex (Engineering Statistics Handbook); and Check No.009772 in the amount of $130.00 to cover the Petition fee.

JC10 Rec'd PCT/PTO 30 NOV 2001

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/980163	PCT/CA00/00998	14081-1US JA/ld

21. ☑ The following fees are submitted:

	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1040.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$890.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$740.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$710.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	$	
Total claims	28 - 20 =	8	x **$18.00**	$ 144.00	
Independent claims	2 - 3 =	0	x **$84.00**	$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$280.00**	$	

TOTAL OF ABOVE CALCULATIONS =	$ 1,034.00	
☑ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2. +	$ -517.00	
SUBTOTAL =	$ **517.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).	$	
TOTAL NATIONAL FEE =	$ **517.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +	$ 40.00	
TOTAL FEES ENCLOSED =	$ **557.00**	
	Amount to be refunded:	$
	charged:	$

a. ☑ A check in the amount of $ 557.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. ______ in the amount of $ ______ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☑ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-5113 . A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Ogilvy Renault
Suite 1600, 1981 McGill College Avenue
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SIGNATURE

James ANGLEHART
NAME

38,796
REGISTRATION NUMBER

File No.: 14081-1US JA/ld

Montreal, Canada
November 27, 2001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	M'Hammed MOUNTASSIR
Serial No:	unknown
Filed:	§371 of PCT/CA00/00998 filed August 28, 2000
§119(e) Priority:	60/152,457 filed September 3, 1999
Title:	METHOD OF OPTIMIZING PARAMETER VALUES IN A PROCESS OF PRODUCING A PRODUCT
Group Art Unit:	unknown
Examiner:	unknown
Agent of Record:	James Anglehart tel.: (514) 847-4244

10081133.120601

PETITION TO MAKE SPECIAL UNDER 37 CFR 1.102 AND MPEP 708.02 (VIII)

The Commissioner for Patents
Washington, D.C. 20231
U.S.A

Sir:

The present application was the object of a prior art search carried out at the United States Patent and Trademark Office shortly before October 12, 2001 by a professional patent searcher in the following field of search:

Class	Subclass/es		Examiners Consulted
703	2, 11, 12	-U. S. and Foreign	Frejd
700	32, 34, 103	-U. S. and Foreign	Foordon
700	28	-U. S. only	
705	1, 7, 10	-U. S. only	Rimell
706	19	-U. S. only	

12/06/2001 UEDUVIJE 00000144 09980163

04 FC:122 130.00 OP

The Commissioner for Patents

PETITION TO MAKE SPECIAL

A detailed discussion of the six (6) references located is provided hereinbelow. These references are enclosed in an IDS filed herewith.

In accordance with MPEP 708.202(VIII), Applicant hereby petitions to make this application special. This Petition also constitutes Applicant's express request for immediate national stage processing under 35USC§371(f). The petition fee of $130 under 37CFR1.17(i) is included. The Commissioner is hereby authorized to charge any deficiency or credit any overpayment regarding the petition fee to deposit account 19-5113.

Applicant According to MPEP 708.02 (VIII), Applicant:

a) requests that this application be made special under 37CFR1.102;

b) consents to elect claims 40 to 51 and related claims if the Examiner finds that a restriction is justified and required **under 37CFR1.475**;

c) submits herewith the results of a prior search;

d) is submitting herewith, a copy of each of the references located;

e) is submitting herewith a detailed discussion which points out, with the particularity required by 37 CFR 1.111(b) and (c), how the claimed subject matter is patentable over the references.

DETAILED DISCUSSION OF THE PRESENT APPLICATION

The present application discloses a method for optimizing process parameters in a process for producing a product. This relates to the general field of experimental design and process improvement. The invention can be applied to any process that is controlled by a set of parameters affecting properties characterizing the product.

A detailed discussion of the state of the art is provided in the Background of the Invention section of Applicant's specification. As an additional immediate reference, Applicant has attached a copy of sections 5.1.1, 5.3.2, 5.3.3.3 and 5.3.3.4 of the Engineering Statistics Handbook (beta version) available on the NIST website. It will be appreciated that the full factorial matrix method is most commonly applied, and that the fractional factorial matrix method is also applied in industry today. Figure 1.1 in section 5.1.1 illustrates clearly how process parameters (i.e. factors) influence the properties of

a product resulting from a process (i.e. responses). In the full factorial matrix method, Table 3.2 in section 5.3.3.3 illustrates clearly how the number of runs required increases exponentially with the number of process parameters (i.e. factors). Table 3.1 of section 5.3.3 illustrates how one may choose an experimental design as a function of the number of process parameters and objective.

In Applicant's invention, the method of producing a product comprises initial steps of optimizing process parameters. The product is characterized by a set of properties. These product properties may be physical properties such as color, weight, strength, resistance, etc. In Applicant's invention, property weights representing an importance of the product properties relative to one another are selected. These property weights are used in conjunction with chosen process parameter values and corresponding product properties to calculate a set of optimal values for the process parameters.

The impact of Applicant's invention is that the number of experimental runs required to calculate the optimal values can be reduced significantly with respect to prior art techniques while maintaining desired accuracy. Tests have shown that Applicant's method will yield optimal values from a number of experimental runs equal to the number of process parameters monitored plus one, and these optimal values are consistently close to optimal values obtained using full or fractional factorial matrix methods. Applicant's method relies on defining the importance of the product properties relative to one another, and in using this data in the calculation of the optimal values from the experimental data of product properties and process parameter values from the reduced number of runs.

SUMMARY OF THE INDEPENDENT CLAIMS

Summary of Claim 25: The method of claim 25 defines assigning property weights to the product properties, and then determining a goal function that is minimized to generate the optimal values for the process parameters. Thus, claim 25 defines a method of producing a product according to a process essentially controlled by a set of

n parameters X_i affecting a set of k properties Y_j characterizing the product. The method comprises:

i. assigning values to a set of k property weights w_j representing relative importance of the properties Y_j for the characterization of the product;
ii. establishing property behavior mathematical relations giving an estimated property Ye_j for each the property Y_j in terms of the parameters X_i from given parameter data and associated property data;
iii. using the property weights w_j to establish a goal function in terms of property weighted deviations between the estimated properties Ye_j and corresponding specified goal values for the properties Y_j;
iv. minimizing the goal function to generate a set of n optimal parameter values for the parameters X_i; and
v. using the set of optimal parameter values in the process to produce the product.

Summary of claim 40: The method of claim 40 defines the steps of conducting a reduced number of experimental runs in combination with determining property weights for the product properties to calculate the optimal values for the process parameters. The method comprises:

a) conducting a number of l of experimental runs of the process each using a selected distinct set of values for the parameters X_i covering substantially all extreme values within a chosen range of values for each one of the parameters X_i, wherein l is at least equal to $n + 1$ and is substantially less than a number used in the Fractional Factorial Matrix method;

b) measuring values for the properties Y_j characterizing the product in each of the l experimental runs, whereby parameter data and associated property data are obtained from the selected distinct set of values for the parameters X_i and the measured values for the properties Y_j, respectively;

c) determining an importance of the properties Y_j for the characterization of the product, comparing the importance of the properties Y_j relative to one another, and assigning values to a set of k property weights w_j representing a relative importance of the properties Y_j for the characterization of the product;

d) calculating a set of optimal parameter values for the parameters X_i using the measured values for the properties Y_j and the assigned values of the set of k property weights w_j; and

e) producing the product using the optimized process parameter values X_i calculated in the previous step.

DETAILED DISCUSSION OF REFERENCES LOCATED DURING SEARCH:

5,119,468 June 2, 1992 Owens

This reference discloses an apparatus and method for controlling a process using a trained parallel distributed processing network. It describes both batch initialization and on-going control of a physical process using a parallel distributed processing network previously trained to stimulate the process, the process being of the type in which inputs have predetermined physical parameters P produce a product having corresponding physical characteristics C. The disclosed method involves: (a) producing a set of goal signals G corresponding to the desired physical characteristics D of the product of the process; (b) determining the error E between the goal signals G and the outputs Y of the network; (c) determining the values of the updated inputs of the parallel distributed processing network that are needed to drive the error E to a

predetermined minimum, and (d) changing the actual physical parameters P of the process to correspond to the updated inputs values producing the minimum error.

However, the disclosed method does not teach assigning values to a set of property weights representing relative importance of the product properties.

5,218,526 June 8, 1993 Mozzo

This reference is discussed in detail in Applicant's specification at page 3, line 16 to page 4, line 11. As mentioned therein, the weightings as taught by Mozzo do not reflect the relative importance of the product properties involved.

5,457,625 October 10, 1995 Lim et al.

This reference discloses a method of maximizing process production rates using permanent constraints. The described method optimizes the relationship of variables associated with a process having inputs and outputs such that the process has controlled variables, manipulated variables, associated variables and disturbance variables, to maximize production rates, and includes the steps of (a) measuring variables of the process comprising controlled, manipulated, associated and disturbance variables; (b) weighting errors associated with at least one controlled variable relative to other controlled variables so as to prioritize errors associated with the controlled variables; (c) optimizing controlled variable deviations from associated setpoints over a predetermined future time horizon based upon manipulated variable differential moves, such as calculating the sum of the squares of the deviations of the controlled variables with the independent variable being the differential moves of the manipulated variable, or calculating the least squares of the deviations of the controlled variables such that the independent variable includes the differential movement of the manipulated variable; (d) suppressing errors associated with at least one future controlled variable by penalizing for large manipulated variable movement for balancing the reduction of future control error against large manipulated variable movement; (e) weighting at least one manipulated variable for reducing deviation of the manipulated variable from a permanent constraint so as to allow preferential movement of at least one of the manipulated variables over another manipulated variable; (f) applying a

constraint deviation variable to effectuate associated variable deviations outside allowable bounds; and (g) controlling the plant operation in accordance with the differential moves determined in steps (b) through (f).

However, the described method does not teach assigning values to a set of property weights representing relative importance of the product properties.

5,500,795 March 19, 1996 Powers et al.

This reference discloses a method and system for monitoring and controlling the performance of a call-processing center. The method involves defining a plurality of performance variables describing measurable properties of the organization, assigning a weighting factor to each of the normalized performance variables to produce a plurality of weighted normalized performance variables, and calculating the efficiency of the organization as a function of the plurality of weighted normalized performance variables.

This reference does not teach a method of producing a product as defined in Applicant's claims 25 and 40, and does not teach assigning values to a set of property weights representing relative importance of the product properties.

5,933,348 August 3, 1999 Kurtzberg et al.

This patent, granted to IBM, discloses a method for optimizing an experimental design used in a manufacturing process, involving: (1) selecting a number of points for the experimental design; (2) selecting a desired maximum number of interactions among process variables to be included in the experimental design; (3) assigning weights to each of the process variables and all the interactions up to the maximum number; (4) creating a sorted list of decreasing weights by ranking all the process variables and the interactions according to the weights; (5) normalizing the weights to aggregate to unity; (6) obtaining the points assigned to each of the process variables and the interactions by multiplying the normalized weights by the number of points; and (7) utilizing the obtained points to optimize the experimental design.

Kurtzberg teaches a method for experimental design, in which the design is influenced by property weights. Kurtzberg teaches using the property weights to choose

the parameters for the runs, in a manner that makes the experimental design more efficient. In Applicant's invention as defined in either claim 25 or claim 40, the property weights are not used to determine the run parameters, but rather, they are used in the calculation that gives the optimized values of the process parameters from the run data, i.e. the process parameter values and product property values obtained from the experimental runs. Kurtzberg therefore does not teach or suggest Applicant's invention as defined in claim 25 or in claim 40.

6,056,781 May 2, 2000 Wassick et al.

This reference is a continuation of US patent 5,740,033 and relates a model predictive controller for a process control system. The process control system includes a real-time executive sequencer projecting a set of future process parameter values to be controlled, and an interactive modeler solving a set of equations as to how the physical process will react to control changes in order to determine an optimized set of control changes. A method involves: projecting a desired set of desired directly controlled parameter values and at least one desired indirectly controlled parameter value over a predetermined control horizon; periodically estimating how the apparatus will react to proposed changes to the value of at least one manipulated parameter over the control horizon, and determining a set of current and future manipulated parameter values which will minimize deviations from the desired set; and causing a process control device in the apparatus to implement the manipulated parameter values.

This reference does not teach a method of producing a product as defined in Applicant's claims 25 and 40, and does not teach assigning values to a set of property weights representing relative importance of the product properties.

CONCLUSION

It is respectfully submitted that none of the references located during Applicant's search discloses or suggests, taken alone or in combination, the method defined in claim 25 or claim 40.

The Commissioner for Patents

PETITION TO MAKE SPECIAL

In view of the foregoing, it is believed that the present application is in good order to be made special, and early consideration to that end is accordingly courteously solicited.

In accordance with 37 CFR 1.97(h), the submission of the present information is not to be construed as an admission that such information is, or is to be considered to be material to patentability.

Respectfully submitted,

M'Hammed MOUNTASSIR

By:

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File No.: 14081-1US JA

Montreal, Canada
November 25, 2001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	M'hammed MOUNTASSIR
Serial No:	unknown
Filed:	§371 of PCT/CA00/00998 filed August 28, 2000
§119(e) Priority:	60/152,457 filed September 3, 1999
Title:	"METHOD OF OPTIMIZING PARAMETER VALUES IN A PROCESS OF PRODUCING A PRODUCT"
Group Art Unit:	unknown
Examiner:	unknown
Agent of Record:	James Anglehart tel: (514) 847-4244

PRELIMINARY AMENDMENT

The Commissioner for Patents
Washington, D.C. 20231
U.S.A

Sir:

Kindly amend the present application as follows:

IN THE SPECIFICATION

Please insert the following paragraph at page 1, before line 4:

This application claims priority of US provisional patent application 60/152,457 filed September 3, 1999.

IN THE CLAIMS

Please cancel claims 1 to 24 filed in this international application, and enter new claims 25 to 52. The fees for eight (8) claims beyond 20 in enclosed in our check for payment of the national stage entry filing fee submitted herewith.

PRELIMINARY AMENDMENT

25. (new) A method of producing a product according to a process essentially controlled by a set of n parameters X_i affecting a set of k properties Y_j characterizing the product, said method comprising:

    i. assigning values to a set of k property weights w_j representing relative importance of said properties Y_j for the characterization of said product;
    ii. establishing property behavior mathematical relations giving an estimated property Ye_j for each said property Y_j in terms of said parameters X_i from given parameter data and associated property data;
    iii. using said property weights w_j to establish a goal function in terms of property weighted deviations between the estimated properties Ye_j and corresponding specified goal values for said properties Y_j;
    iv. minimizing the goal function to generate a set of n optimal parameter values for said parameters X_i; and
    v. using said set of optimal parameter values in said process to produce said product.

26. (new) A method according to claim 25, wherein said product is a composition of matter, said set of optimal parameter values characterizing an optimal formulation for the composition.

27. (new) A method according to claim 26, wherein said product is a pharmaceutical product, said set of optimal parameter values characterizing an optimal formulation for the pharmaceutical product.

28. (new) A method according to claim 25, wherein the values for said property weights w_j are obtained using an algorithm based on an analytic hierarchy process.

PRELIMINARY AMENDMENT

29. (new) A method according to claim 28, wherein said given property data are obtained through a number l of experimental runs of said process using said given parameter data, each said run using a distinct set of values for said given parameter data.

30. (new) A method according to claim 29, wherein said number of experimental runs of said process each uses a selected distinct set of values for said parameters X_i covering substantially all extreme values within a chosen range of values for each one of said parameters X_i, wherein l is at least equal to n + 1 and is substantially less than a number used in the Fractional Factorial Matrix method.

31. (new) A method according to claim 27, wherein the values for said property weights w_j are obtained using an algorithm based on an analytic hierarchy process.

32. (new) A method according to claim 31, wherein said given property data are obtained through a number l of experimental runs of said process using said given parameter data, each said run using a distinct set of values for said given parameter data.

33. (new) A method according to claim 32, wherein said number of experimental runs of said process each uses a selected distinct set of values for said parameters X_i covering substantially all extreme values within a chosen range of values for each one of said parameters X_i, wherein l is at least equal to n + 1 and is substantially less than a number used in the Fractional Factorial Matrix method.

34. (new) A method according to claim 25, wherein said goal function is expressed as follows:

$$G(X_i,...X_n) = \sum_{j=1}^{k} w_j^2 (Ye_j - O_j)^2$$

wherein O_j are said specified goal values for said properties Y_j.

35. (new) A method according to claim 34, wherein said minimizing step is performed by successive iterations of:

$$G(X_1,...,X_n) = \sum_{i=1}^{k} [f_i(X_i,...,X_n)]^2.$$

36. (new) A method according to claim 35, wherein said goal function is minimized according to one or more specified ranges (a_i, b_i) wherein $a_i < X_i < b_i$ for one or more of said optimal parameter values.

37. (new) A method according to claim 25, further comprising the steps of:
performing experimentally said process using said set of optimal parameters values to obtain corresponding experimental values for said properties Y_j;
ranking said set of optimal parameters values over predetermined alternative sets of parameters values for said X_i.

38. (new) A method according to claim 37, wherein said ranking step is performed using an algorithm based on an analytic hierarchy process.

39. (new) A method according to claim 37, further including the step of:
incorporating said set of optimal parameters values and said corresponding experimental values for said properties Y_j respectively into said given parameter and associated property data;
repeating said steps ii) to iv) to generate a new set of optimal parameters values for said parameters X_i.

PRELIMINARY AMENDMENT

40. (new) A method of producing a product using optimized process parameter values, said process being essentially controlled by a set of n parameters X_i characterizing a formulation for said product, said parameters X_i affecting a set of k properties Y_j characterizing the product, said method comprising:

a) conducting a number of l of experimental runs of said process each using a selected distinct set of values for said parameters X_i covering substantially all extreme values within a chosen range of values for each one of said parameters X_i, wherein l is at least equal to n + 1 and is substantially less than a number used in the Fractional Factorial Matrix method;

b) measuring values for said properties Y_j characterizing the product in each of said l experimental runs, whereby parameter data and associated property data are obtained from said selected distinct set of values for said parameters X_i and said measured values for said properties Y_j, respectively;

c) determining an importance of said properties Y_j for the characterization of said product, comparing said importance of said properties Y_j relative to one another, and assigning values to a set of k property weights w_j representing a relative importance of said properties Y_j for the characterization of said product;

d) calculating a set of optimal parameter values for said parameters X_i using said measured values for said properties Y_j and said assigned values of said set of k property weights w_j; and

e) producing said product using said optimized process parameter values X_i calculated in the previous step.

PRELIMINARY AMENDMENT

41. (new) A method according to claim 40, wherein said product is a pharmaceutical product, and said process is a formulation of said product.

42. (new) A method according to claim 41, wherein said step of calculating comprises:
establishing property behavior mathematical relations giving an estimated property Ye_j for each said property Y_j in terms of said parameters X_i from said parameter data and associated property data;
using said property weights w_j to establish a process goal function in terms of property weighted deviations between the estimated properties Ye_j and corresponding specified goal values for said properties Y_j; and
minimizing the process goal function to generate a set of optimal parameter values for said parameters X_i.

43. (new) A method according to claim 42, wherein the values for said property weights w_j are obtained by an algorithm based on an analytic hierarchy process.

44. (new) A method according to claim 40, wherein $l = n + 1$.

45. (new) A method according to claim 42, wherein $l = n + 1$.

46. (new) A method according to claim 43, wherein $l = n + 1$.

47. (new) A method according to claim 41, wherein said goal function is expressed as follows:

i. $G(X_i,...X_n) = \sum_{j=1}^{k} w_j^2 (Ye_j - O_j)^2$

wherein O_j are said specified goal values for said properties Y_j.

48. (new) A method according to claim 47, wherein said minimizing step is performed through successive iterations.

49. (new) A method according to claim 48, wherein said goal function is minimized according to one or more specified ranges (a_i, b_i) wherein $a_i < X_i < b_i$ for one or more of said optimal parameters values.

50. (new) A method according to claim 41, further comprising the steps of:

    f) performing experimentally said process using said set of optimal parameters values to obtain corresponding experimental values for said properties Y_j;

    g) ranking said set of optimal parameters values over predetermined alternative sets of parameters values for said X_i.

51. (new) A method according to claim 50, wherein said ranking step is performed through an algorithm based on an analytic hierarchy process.

52. (new) A method according to claim 41, further including the steps of:

    h) incorporating said set of optimal parameters values and said corresponding experimental values for said properties Y_j respectively into said given parameter and associated property data;

    i) repeating said steps a), b) and d) to generate a new set of optimal parameters values for said parameters X_i.

The Commissioner for Patents

PRELIMINARY AMENDMENT

REMARKS

The claims have been amended to remove any multiple dependencies, and to provide two independent method claims as disclosed in Applicant's specification.

Respectfully submitted,

M'Hammed MOUNTASSIR

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09/980163

JC10 Rec'd PCT/PTO 30 NOV 2001

21 PRTS

METHOD OF OPTIMIZING PARAMETER VALUES IN A PROCESS OF PRODUCING A PRODUCT

BACKGROUND OF THE INVENTION

Field of the invention

The invention relates to the process optimization field, and more particularly to a method of optimizing parameter values in a process of producing a product which is characterized by properties affected by the selected parameter values. This invention is applicable in different industries, such as the pharmaceutical, chemical, cosmetics, plastics, petrochemical, agriculture, metallurgy and food industries, as well as many other commercial and industrial applications.

Description of prior art

Processes for production of complex compositions such as those found in many pharmaceutical products generally require the mixing of many ingredients according to specific process parameters regarding formulation and production technology, to provide the product with properties at a level offering satisfactory performance according to predetermined specifications. In such complex production processes, it is not unusual that some process parameters involved exhibit interfering effects on the desired properties, further complicating the process design. Where possible, the designer may try to adapt the set of process parameters from known data derived from previous similar processes, and/or rely on conventional trial-and-error experimental schemes to optimize the set of process parameters values, in order to meet the product specifications. However, as the processes become more complex, optimization in such multidimensional space with high accuracy requirements turns out to be an extremely difficult task, even for the highly skilled designer. That limitation is particularly problematic in the design of pharmaceutical products, where one or more active substances mixed with a variety of excipients (e.g. carriers) must be produced in the form of a

stable and highly effective standard delivery system such as a tablet, capsule, suspension, cream or injection, or even controlled release systems such as skin carriers and implants.

In the past years, many techniques have been developed to assist the process designer or formulator in optimizing values of parameters governing processes. These techniques aim at quantify existing relations between parameters and associated desired product performance characteristics. A conventional technique known as the Full Factorial Matrix (FFM) method consists of statistically deriving a behavior relations for the properties from a set of experimental runs of the process using selected initial values for the parameters. The established model being generally nonlinear, optimized parameter values are then derived using an optimization method such as the Multisimplex method described in "*Practical Methods of Optimization*" J, Wiley & Sons, Chichester, 2d, (1987), which essentially consists of linearizing the behavior functions related to the parameters according to straight lines or planes of different random directions. For any given property behavior relation of n parameters to be optimized in order to either minimize or maximize that behavior relation with or without constraints on the parameter values, a recursive estimation of the property is then performed using an initial set of parameter values according to a selected direction, until the obtained value for the property does not significantly vary in that direction. Then, a last unfavorable set of parameters is used as a new starting point for a following recursive estimation according to a different direction. Successive recursive estimation steps are performed until the resulting value for the property no longer significantly vary in any new direction. When applied to a model comprising a plurality of property behavior relations, the Multisimplex method allows a unique objective function to be created by proper transformation of the relations to adapt to different scales and/or units and by associating a relative importance weight to each property, either subjectively or through fuzzy logic algorithms.

The known optimization processes based on Full Factorial Matrix-Multisimplex methods suffer from several drawbacks. As a general rule, the number of experimental runs required to obtain a model of sufficient reliability is proportional to the total number of significant parameters involved. Therefore, the cost and time frame of the experimental work will therefore be essentially proportional to the number of runs required. Although a variant of the method known as the Fractional Factorial Matrix has been proposed in order to reduce the number of runs to be performed, the provided reduction of experimental runs may not significantly reduce the total cost and time frame of the work required to complete the design of a complex product involving many production technologies. While adequate formulations complying with constraints imposed on the parameter values can nevertheless be obtained, these formulations generally cannot be qualified as optimal when comparing actual property performance with desired property values set forth in the product specifications.

A technique which attempts to improve parameter optimization in process design is disclosed in European Patent Office laid-open patent application publication number 0,430,753 dated June 5, 1991 and in US patent No. 5,218,526 issued on June 8, 1993 to Mozzo. According to the technique in Mozzo, from a set of property relations expressed in terms of parameters which is obtained by standard statistical methods using the results of a number of experimental runs of the process, a corresponding set of property relations expressed in terms of weighted parameters is derived. For each actual value of a parameter, a first weighting is expressed as the ratio of: (a) the deviation of the actual value from the mean value of the parameter over the experimental range, on (b) the range between extreme values for that parameter over the experimental range. Then, a goal function is established in term of deviations between weighted values of property values as estimated by the property relations and corresponding weighted values of specified goal values for the properties. For each goal value of a property, a second weighting is expressed as the

ratio of: (a) the deviation of the actual value from the mean value of the property over the experimental range, on (b) the range between extreme values for that property over the experimental range. Then, according to a recursive geometric algorithm aimed at successively minimizing the established goal function, a set of optimal parameter values is generated. While being an improvement over the conventional Full/Fractional Factorial Matrix - Multisimplex methods regarding the capability to consider specified goal values for the properties, the weightings as taught by Mozzo do not reflect the relative importance of the properties involved, and that limitation may therefore affect the convergence of the algorithm toward an optimal solution.

A review of modern techniques and software systems for the design of pharmaceutical product formulations is given in "*Intelligent Software System For Pharmaceutical Product Formulation*" R.C. Rowe, Pharmaceutical Technology, March 1997. In that paper, expert systems, rule induction algorithms, case-based reasoning algorithms, neural networks and genetic networks are presented as modern tools for supporting formulation design, and a number of available software systems using some of these tools are summarized. As indicated in the Rowe paper, although a knowledgeable expert system could be a powerful tool to assist the process designer in the formulation task, its development is generally a high risk, time consuming and expensive process. Rule induction is a knowledge-based algorithm which allows hierarchical classification of objects, using statistical methods which are found generally effective only if the input data is continuous, which is often not the case in practice. Moreover, since rule induction is limited to establishing whether or not a given object is close to another, it generally cannot provide an optimal solution. Case-based reasoning is a knowledge-based iterative technique which can be used to design formulations, which consists of matching the desired specifications for the product with the specifications of the most relevant known formulation(s), and adapting the selected formulation(s) as

necessary, followed by an evaluation. Although effective for optimizing the parameters of a variant process from a family of similar processes and corresponding formulations, case-based reasoning generally cannot be used where the design of a significantly different formulation is contemplated. As to neural networks, in which each neuron input is modified by a weight associated with that neuron, they appear to be effective tools for assisting formulation design only in cases where no constraint applies on either the parameter or property values, such cases being rarely found in practice. Finally, regarding the genetics algorithms, they are cyclic methods based on Markov chains for predicting from a starting point a solution likely to result from a sequence of operations, in order to allow making changes to obtain a desired solution. Since these changes are generally made arbitrarily, in most cases, the resulting solution cannot be considered as optimal.

SUMMARY OF THE INVENTION

It is therefore an object of the present invention to provide a systematic method of optimizing parameter values in a process for producing a product which minimizes the number of experimental runs required to obtain an optimal solution complying with the product specifications.

According to the above object, from a broad aspect of the present invention, there is provided a method of optimizing parameter values in a process of producing a product, the process being essentially controlled by a set of n parameters X_i affecting a set of k properties Y_j characterizing the product. The method comprises the steps of: i) assigning values to a set of k property weights w_j representing relative importance of the properties Y_j for the characterization of the product; ii) establishing property behavior mathematical relations giving an estimated property Ye_j for each property Y_j in terms of the parameters X_i from given

parameter data and associated property data; iii) using the property weights w_j to establish a goal function in terms of property weighted deviations between the estimated properties Ye_j and corresponding specified goal values for the properties Y_j; and iv) optimizing the goal function to generate a set of n optimal parameter values for the parameters X_i.

According to a further broad aspect of the present invention, there is provided a method of producing a pharmaceutical product using optimized process parameter values, the process being essentially controlled by a set of n parameters X_i characterizing a formulation for the product, the parameters X_i affecting a set of k properties Y_j characterizing the product. The method comprises the steps of: a) conducting a number of l of experimental runs of the process each using a selected distinct set of values for the parameters X_i covering substantially all extreme values within a chosen range of values for each one of the parameters X_i, wherein l is at least equal to n + 1 and is substantially less than a number used in the Fractional Factorial Matrix method; b) measuring values for the properties Y_j characterizing the product in each of the l experimental runs, whereby parameter data and associated property data are obtained from the selected distinct set of values for the parameters X_i and the measured values for the properties Y_j, respectively; c) determining an importance of the properties Y_j for the characterization of the product, comparing the importance of the properties Y_j relative to one another, and assigning values to a set of k property weights w_j representing a relative importance of the properties Y_j for the characterization of the product; d)calculating a set of optimal parameter values for the parameters X_i using the measured values for the properties Y_j and the assigned values of the set of k

property weights w_j; and e) producing the pharmaceutical product using the optimized process parameter values X_i calculated in the previous step.

BRIEF DESCRIPTION OF THE DRAWING

The invention will be better understood by way of the following detailed description of a preferred embodiment with reference to the appended drawings, in which:

Fig. 1 is a block diagram of a software system that can be used to carry out the method according to the present invention according to the preferred embodiment; and

Fig. 2 is a flow chart representing the preferred embodiment of the method according to the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

In the following description, a preferred embodiment of the present invention applied to product formulation design will be described. However, it is to be understood that the present invention can be also be used to optimize parameter values of processes related to the production of many types of products which cannot be associated with a formulation, while being characterized by a number of properties affected by process parameters, such as biotechnological products, electronic components, etc.

Referring now to Fig. 1, there is generally designated at 10 a computer system which is programmed to carry out a method according to the present invention. The system preferably comprises a knowledge base 12 where prior formulation/process data and competing products data are stored. For the purpose of pharmaceutical formulation design, knowledge base 12 contains process data related to ingredient proportions, experimental conditions and results over time, production technologies used, etc. The system 10 further comprises a property weighting module 14 which generates a weight value for each one of a number k of identified properties according to an initial modeling of the problem and property

comparison data presented to the module 14. System 10 further comprises an evaluation module 18 fed by the property weights generated by module 14, to generate a global relative importance vector of dimension $[k]$ for the k properties. System 10 is provided with an experimental data entry module 16 through which property values obtained from experimental runs using different sets of parameter values for the process can be entered and stored for later use by several modules of system 10. Linked to receive data from modules 12, 14 and 16, is an evaluation module 18 which can generates a ranking of the sets of property values selected from the knowledge base and the optimal set of parameter values obtained through optimization. System 10 further comprises a parameters reduction module 22 to retain only those parameters having a significant effect on the considered properties. Module 22 is particularly useful in cases where the number of parameters involved is relatively large, usually greater than 8 where a computer provided with a standard high-performance microprocessor is used. The S-Plus™ statistical software from MathSoft may be used in module 22 to carry out the Stepwise method to select the variables . System 10 is further provided with a parameter interaction module 20, the function of which consists of identifying by statistical analysis from experimental data, which remaining parameters are significantly correlated. The S-Plus statistical software from MathSoft can also be used to program module 20 in which the appropriated correlation methods are applied to the data. It is to be understood that module 20 is unnecessary where all parameters are independent one another.

Modules 16, 20 and 22 are linked to a property behavior models module 24 that uses experimental data, parameter interaction data and remaining significant parameters for determining an optimal mathematical model for each property which is likely to better estimate that property. The model data as generated at module 24 is fed to a property behavior relation module 26 that also receives experimental data from module 16 to statistically estimate polynomial coefficients to be incorporated within the

established property behavior models, thereby generating a behavior relation for each property. The S-Plus statistical software from MathSoft may be used to program module 26 to apply the appropriate regression methods to the data. System 10 is further provided with a goal function module 28 linked to property weighting module 14 and property behavior relation module 26 to generate, from specified goal values for the properties, a goal function in term of property weighted deviations between properties as estimated by the behavior relations and the corresponding specified goal values for these properties.

An optimization module 30 is provided to optimize the goal function as established by module 28 through successive iterations and according to the type of each variable (discrete or continuous) and according to one or more ranges specified as constraints imposed on one or more optimal parameter values. Module 30 can be programmed using Matlab™ software supplied by The Math Works Inc to implement network optimization methods. Optimization module 30 is linked to the experimental data entry module 16 to transfer thereto the generated set of optimal parameter values, which module 16 also stores the actual property values obtained from an experimental run based on the set of optimal parameter values. All experimental data is then transferred to the evaluation module 18 as mentioned before.

A preferred embodiment of an optimization method according to the present invention will now be described with reference to Figs. 1 and 2. As illustrated in the general flow chart shown in Fig. 2, the method comprises a first step 40 of assigning values to a set of k property weights w_j representing relative importance of the k properties Y_j for the characterization of the product, which properties are likely to be affected by the parameters of the process, from a modeling of the problem expressed as a hierarchical tree of these properties. Initial modeling and weight value generation are preferably performed using a method known as analytic hierarchy process (AHP), which was first proposed by T.W. Saâty, and

more recently described in "*Using The Analytic Hierarchy Process For Decision Making In Engineering Applications: Some Challenges*" Triantaphyllou et al, International Journal of Industrial Engineering: Application and Practice, Vol. 2, No. 1, pp. 35-44, (1995), which is incorporated herein by reference.

The AHP method consists of building a hierarchical tree from all properties, with one or more hierarchical levels depending on existing relations between the properties. For each level, a pair-wise comparison matrix is built between the properties of this level and presented at an input of the parameters weighting module 14 shown in Fig. 2, which executes in step 40. For each pair-wise comparison, the normalized eigenvector is derived associated with the higher eigenvalue. The components of this eigenvector give the relative importance of each property called the local weight. Finally, the above normalized vectors are combined to find the global weight for each property.

In a parallel direction, each pair-wise comparison is associated with a consistency index reflecting the transitivity relation between all comparison by pairs given by the formulator. Multi-criteria analysis software which is commercially available, such as Expertchoice™, Criterium™ or Ergo™, may be used to program module 14. For example, to one or more m main properties classified at a first (higher) level, may correspond one or more groups of properties classified at a second (lower) level, the latter properties being therefore identified as sub-properties. For each main property associated with a group of p sub-properties, a matrix of dimension $[p+1 \times p+1]$ is built and filled, as a result of a pair-wise comparison between each property and sub-property, using relative importance values selected from a standard AHP scale. Next, a suitable algorithm performed by parameter weighting module 14 consists of first calculating the higher eigenvalue of the resulting numerical matrix, and then deriving a normalized relative importance vector of dimension $[p+1]$ by an estimation of the left principal eigenvector of that matrix associated

with the calculated main eigenvalue of the input matrix. The above algorithm is then applied to compare the m main properties of the higher level, from a pair-wise comparison matrix of dimension $[m \times m]$ from which a normalized relative importance vector of dimension $[m]$ is derived. Finally, the above normalized vectors are combined according to the hierarchical relations to generate a global relative importance weight vector for the k properties of dimension $[m+\sum p]$ or $[k]$. In practice, it is generally appropriate to retain only each group of sub-properties without the corresponding main property, the sum of the weights related to the retained k properties/sub-properties being always equal to unity.

According to the next step, namely step 42, parameter data and property data values are provided, which data is obtained from experimental runs using different sets of parameter values for the process, the various values for each parameter being preferably selected according to an expected operation range within which an optimal parameter value is likely to be found. The parameters X_i used in the experimental runs should cover the extremes of the expected operational range for each parameter. Generally, the number of formulation combinations required to determine an optimal formulation depends on many factors among which the more important ones are: 1) the formulation designer experience; 2) complexity of the formulation; 3) the availability of literature and experimental data available on the desired product; and 4) the analytical laboratory workload and throughput. According to the method of the present invention, the minimal number of experimental runs l to perform has been found to be equal to $n+1$, wherein n is the number of relevant parameters involved. A greater number of runs is certainly possible. Step 42 is performed by experimental data entry module 16 shown in Fig. 1.

The method then comprises a step 44 of establishing property behavior mathematical relations linking the properties with the parameters and interactions thereof, in polynomial form. These property behavior

relations provide an estimated property Ye_j for each of the k properties Y_j in terms of a number n of parameters X_i from the parameter data and associated property data provided at step 42. Step 44 is typically comprised of four sub-steps, namely 1) a parameters reduction step performed by module 22, 2) a parameters interaction analysis step performed by module 20, 3) a property behavior modeling step performed by module 24, and 4) a property behavior relations generating step performed by module 26, as shown in Fig. 1. As to sub-step 1), to provide a more efficient algorithm, from an initial number of identified parameters, the most significant parameters, i.e. those significantly affecting each property, are identified to generate a reduced number n of significant parameters, especially where the initial number of identified parameters is greater than 8, as mentioned before. For that purpose, a statistical analysis algorithm can be used, which is based on parameter correlation calculations using parameter and property experimental data provided at prior step 42. Having obtained data related to l experimental runs involving an initial number p of parameters and a number k properties Y_i, each correlation factor contained in the correlation matrix is retained as significant whenever it complies with a predetermined condition in the following form:

$$a < \rho_{ij} < b \quad \text{or} \quad -c < \rho_{ij} < -d \qquad (1)$$

wherein a,b,c and d are predetermined limit values, typically set as follows:

$$0.5 < \rho_{ij} < 0.95 \quad \text{or} \quad -0.95 < \rho_{ij} < -0.5. \qquad (2)$$

The parameters associated with the retained correlation factors form the reduced set of n parameters.

It can be also shown that a minimum number l of runs at least equal to $n+1$ is required to obtain reliable parameters estimation. Then, parameter interactions, that are in the form X_iX_j with $i \neq j$ and which are significant, can be identified using the above relations (1), with the

suggested specific ranges given in (2). The values for X_i from the l experimental runs are combined with the retained correlation factors ρ_{ij} to form a final matrix W, with each element of the first column being equal to unity for the purpose of following sub-step 4). As to sub-step 3), it consists of establishing, for each property Y_j , a best model in terms of retained parameters and parameter interactions. A standard variance analysis is carried out to confirm relevancy of all parameter coefficients and parameter interaction coefficients, and to select by successive variance analysis operations through the use of modules 24, 20 and 22, a suitable model amongst different predetermined models of upgraded degrees, whenever difference in performance between a given model of degree r and a following model of degree r+1 is found to be not significant. The resulting best model is taken along with matrix W and property experimental data in matrix Y, as inputs for following sub-step 4) aimed at generating property behavior relations for each property Y_j. A matrix C of coefficient values is given by the matrix:

$$C = \left(W^T W\right)^{-1} \times W^T \times Y \qquad (8)$$

having a dimension of $[m,k]$, wherein $m = n + t + 1$, t being the number of parameters interactions $X_i X_j$. Hence, estimated property values are given by:

$$Ye = C^T X = \begin{cases} Y_1 = f_1(X_1,\dots,X_n,\dots,X_i X_j) \\ \dots \\ Y_j = f_j(X_1,\dots,X_n,\dots,X_i X_j) \\ \dots \\ Y_k = f_k(X_1,\dots,X_n,\dots,X_i X_j) \end{cases} \qquad (9)$$

A following step 46 as shown in Fig. 2 aimed at generating a goal function is carried out by the module 28 shown in Fig. 1, from the set of k property weights w_j produced at step 40, from the property behavior

relations produced at step 44 and from the specified goal values for the properties Y_j. The basic goal vector can be expressed as follows:

$$g(X_i) = g(X_1,\ldots,X_n,\ldots,X_iX_j) = [w_1(Y_1 - O_1),\ldots,w_k(Y_k - O_k)] \qquad (10)$$

wherein O_i is the specified goal values for the properties Y_i, with $i = 1,\ldots,k$.

The goal function to be minimized may be expressed as follows:

$$G(X1,\ldots Xn) = g^T * g = \sum_{i=1}^{k} w_i^2 (Y_i - O_i)^2 \qquad (11)$$

which goal function is expressed in terms of property weighted deviations between estimated values Ye_j for the properties Y_j and corresponding specified goal values O_i for the same properties Y_j. A next step 48 as shown in Fig. 2 therefore consists of minimizing the goal function G to obtain a set of optimal parameter values for the parameters X_i, which step 48 is performed by module 30 shown in Fig. 1. Optimization step 48 generally can consider constraints on the parameter values in the form of one or more ranges, typically in a form (a_i,b_i) wherein $a_i < X_i < b_i$, within which optimal parameter values shall be found, according to the type of each variable (i.e. discrete such as binary values, or continuous).

The "G" goal function is determinated by experimentation. The optimization of the "G" function is a step by step procedure. The first step is to obtain the behavior laws with the best fit between the experimental data and their corresponding ideal value factor.

The second step, the optimization is based on a initial point.

$$X^0 = [X_1^0, X_2^0, \ldots, X_n^0]$$

and

$$X^{k=1} = X^k - \alpha Hg\big|_{X=X^k}$$

where

$$g = {}^{\nabla}G = gradientG$$

H= the Hessian of G

And based on the following goal function, we use the dimension reduction method by successive iterations

$$G(X_1,\dots,X_n)=\sum_{i=1}^{k}\left[f_i(X_i,\dots,X_n)\right]^2$$

these iterations passed by

$$f_i(X_1,\dots,X_{n-1})=0$$

if $i=1,\dots,k-1$

and

$$X_n=f_k(X_1,\dots,X_{n-1})$$

Now the goal function can be:

$$G(X_1,\dots,X_n)=G(X_1,\dots,X_{n-1},f_k(X_1,\dots,X_{n-1}))$$

We observe a perfect overlap between the two goal functions and on the stationary point the goal function will be;

$$\frac{\partial G(X_r)}{\partial X_i}=\left[\frac{\partial G(X)}{\partial X_i}+\frac{\partial G(X)}{\partial X_n}\frac{\partial f_k(X_1,\dots X_{n-1})}{\partial X_i}\right]_{X_n=f_k(X_1,\dots,X_{n-1})}$$

These equations supply the maxima and minima of the goal $f_k(X_1,\dots,X_{n-1})$ functions including the maxima and minima from the starting goal function.

This mathematical approach induces a reduction of the dimension of the variables, consequently we pass from "n" variables to "n-1" variables. In the actual case, we start with the most important variables from the behavior laws with the highest weight values of the factor.

This approach is known under the name of network optimization, in this case the network nodes are built by the optimal values of the variable by decreasing order of the factor's rank.

After the iterative optimization step 48 is completed, although the set of optimal parameter values $X0_i$ obtained can generally be considered as the solution to recommend, that solution is preferably evaluated amongst other alternative solutions by following steps 50 and 52 as shown in Fig. 2. At step 50, an experimental run of the process is carried out using the obtained set of optimal parameter values, to obtain experimental values for the k properties Y_i. The optimal property values $X0_i$ and associated experimental property values are then evaluated at step 52 to obtain ranking thereof amongst a number m of other alternative solutions, which may have been selected from knowledge base 12 shown in Fig. 1. This evaluation is preferably performed by a complete AHP process algorithm, using the set of k property weights w_j as previously obtained through step 40.

CONCRETE APPLICATION

An example illustrating an application of the method according to the present invention in the pharmaceutical field will now be described.

Formulation and production process for enalapril maleate tablets were optimized in order to provide a drug product with satisfactory biological performance as well as stability when packaged and stored under ICH (International Conference on Harmonization) conditions. Three (3) independent formulation and process parameters $(n = 3)$ were identified as having an impact on the stability of the drug product: 1) the degree of drug neutralization during granulation (X_1) ; 2) the manufacturing technology (X_2) ; and 3) The drug-to-excipient ratio in the formulation, i.e. dose strength (X_3).

As to the degree of drug neutralization during granulation (X_1), it was classified as either complete, partial or no neutralization. In the case

of complete neutralization, the drug and the alkaline agent were both added to the granulation fluid, i.e. water. Therefore, the alkaline agent neutralized the drug prior to its addition to the powder blend for the granulation procedure. In partial neutralization, both the drug and the alkaline agent were added to the powder blend, blended and water added as the granulation fluid for the granulation procedure. When water and/or alkaline agent were not added to the formulation, the drug was not neutralized. The level of water added as well as the drug-to-alkaline agent ratio were kept constant for all of the formulations. The level of the alkaline agent was determined by the stoichiometry of the reaction.

The manufacturing technology (X_2) was either wet granulation ($X_2 = 0$) or direct compression ($X_2 = 1$). These two technologies are used worldwide for the manufacturing of probably more than 90% of all of the solid oral dosage forms. In the wet granulation technology, the drug and other functional materials added to impart good processing attributes to the drug, often called excipients, are first blended together and agglomerated into larger particles by the addition of a granulating fluid. The role of the granulating fluid is to promote the development of adhesive forces between the materials required for the agglomeration process. After granulation, the granulating fluid is removed by drying. When a direct compression approach is selected as a manufacturing method, the drug is first blended with the excipients and tablets produced without the use of a granulating fluid.

As to the dose strength (X_3), four doses of the product were developed, which were obtained by using two formulations with different drug-to-excipient ratios (continuous parameter values) compressed at different tablet weights.

A total of nine (9) experimental runs involving different formulations based on a combination of the three parameters were prepared, as shown in Table 1.

Run	X_1	X_2	X_3
1	1.73	1	3.33
2	1.73	0	3.33
3	1.73	0	3.33
4	0	0	3.33
5	0	1	3.33
6	6.9	1	13.3
7	6.9	0	13.3
8	6.9	0	13.3
9	0	0	13.3

TABLE 1

The nine formulations covered all of the six (6) possible combinations for the wet granulation technology and three (3) combinations of direction compression. Tablets were manufactured by using enalapril maleate with USP/NF and EP excipients. In the direct compression technology, there is not a sufficient amount of moisture to dissolve all the drug and alkaline agent and provide for any significant neutralization reaction. However, excipients do contain a certain level of adsorbed free moisture capable of creating a microenvironment where small quantities of the drug and alkaline agent can be dissolved and become available for the neutralization reaction. These phenomena could be responsible of the appearance of physical as well as chemical stability problems and where taken into account by evaluating three (3) formulation combinations. The nine (9) formulation combinations where prepared and the tablets were stored in opened containers at 25°C/60%RH and 40°C/75%RH for a 2-week period. These open container studies are typically conducted during the early formulation development phases of a product to purposely accelerate physical and chemical changes in formulations in order to select

the lead candidate, i.e., the formulation with the best stability profile. After the 2-week time period, the tablets were removed from the environmental chambers and sent to the analytical department for their performance evaluation. The performance of the formulations was determined by measuring ten (k=10) properties as a function of time and temperature, which properties were selected as follows, according to a hierarchical tree comprising properties and sub-properties:

- Y11, Y12, Y13: % drug dissolved at 5, 15, and 30 min. (sub-properties of Y1);
- Y2: % of cyclization product at time zero;
- Y31, Y32: % cyclization product after 2 weeks at 25°C/60%RH and at 40°C/75%RH (sub-properties of Y3);
- Y4: differential between theoretical and actual assay in mg at time zero;
- Y51, Y52: differential between theoretical and actual assay in mg after 2 weeks at 25°C/60%RH and at 40°C/75%RH (sub-properties of Y5);
- Y6: % hydrolytic product after 2 weeks at 40°C/75%.

Applying the AHP process with the standard scale for these properties, the decision matrixes given in Table 2 for the properties and in Tables 3, 4 and 5 for the sub-properties were built.

Goal	Y1	Y2	Y3	Y4	Y5	Y6
Y1	1.0	(5.0)	(5.0)	3.0	1.0	(5.0)
Y2		1.0	(5.0)	1.0	(3.0)	(7.0)
Y3			1.0	7.0	1.0	1.0
Y4				1.0	(7.0)	(7.0)
Y5					1.0	(1.0)
Y6						1.0

TABLE 2

Y1	Y11	Y12	Y13
Y11	1.0	7.0	9.0
Y12		1.0	3.0
Y13			1.0

TABLE 3

Y3	Y31	Y32
Y31	1.0	(5.0)
Y32		1.0

TABLE 4

Y5	Y51	Y52
Y51	1.0	(5.0)
Y52		1.0

TABLE 5

From the decision matrixes, the following weight values for the k=10 properties/sub-properties are given in Table 6, the sum of the weights being equal to unity.

w_1 (Y11)	w_2 (Y12)	w_3 (Y13)	w_4 (Y2)	w_5 (Y31)	w_6 (Y32)	w_7 (Y4)	w_8 (Y51)	w_9 (Y52)	w_{10} (Y6)
0.060	0.011	0.005	0.098	0.046	0.230	0.039	0.034	0.171	0.305

TABLE 6

Experimental property data that were obtained from nine (9) runs of the process using the selected nine (9) combinations of parameter values of Table 1, are given in Table 7.

Run	Y11	Y12	Y13	Y2	Y31	Y32	Y4	Y51	Y52	Y6
1	90.40	102.7	102.1	0.88	1.210	15.06	0.080	(0.01)	0.660	4.260
2	91.20	95.10	95.80	0.63	1.070	3.510	0.120	0.020	0.340	5.350
3	86.80	100.4	101.6	0.90	0.850	0.720	0.080	0.030	0.110	3.670
4	94.00	96.70	97.20	0.85	1.340	16.88	0.300	0.160	0.780	2.590
5	75.40	106.2	107.1	0.83	1.350	22.54	(0.08)	0.040	0.960	3.570
6	94.70	98.20	98.30	0.54	1.110	8.600	0.380	0.270	2.200	6.730
7	90.20	98.70	98.40	0.64	1.670	5.980	0.310	0.290	1.750	7.710
8	51.70	100.4	100.8	0.50	0.75	0.750	(0.04)	(0.14)	0.310	3.580
9	84.90	95.30	95.20	0.55	0.11	0.110	0.930	0.740	2.210	1.450

TABLE 7

Since $n = 3 < 8$, the parameter reduction step is not required for the purpose of the instant case. As to the statistical analysis of parameters interaction, since a correlation factor ρ_{13}=0.7013 for the X_1X_3 interaction was calculated, that interaction can be considered as significant since the condition $0.5 < \rho_{13} < 0.95$ is satisfied. The following property behavior relations were established:

$$Y11 = 81.916 + 4.56X_1 + 4.074X_2 + 0.224X_3 - 0.423X_1X_3;$$

$$Y12 = 101.93 - 1.45X_1 + 3.81X_2 - 0.51X_3 + 0.14X_1X_3;$$

$$Y13 = 102.16 - 14.8X_1 + 3.46X_2 - 0.52X_3 + 0.14X_1X_3;$$

$$Y2 = 0.92 - 0.025X_1 + 0.025X_2 - 0.028X_3 + 0.0018X_1X_3;$$

$$Y31 = 1.42 - 0.23X_1 + 0.057X_2 - 0.03X_3 + 0.019X_1X_3; \qquad (18)$$

$$Y32 = 17.18 - 8.78X_1 + 8.15X_2 - 0.46X_3 + 0.56X_1X_3;$$

$$Y4 = -0.15 + 0.0193X_1 - 0.022\ X_2 + 0.08X_3 - 0.0091X_1X_3;$$

$$Y51 = -0.135 - 0.028X_1 + 0.0385X_2 + 0.066X_3 - 0.0045X_1X_3;$$

$$Y52 = 0.00089 - 0.256X_1 + 0.63X_2 + 0.166X_3 + 0.008X_1X_3;$$

$$Y6 = 3.24 + 0.9X_1 + 0.57X_2 - 0.13X_3 - 0.02\ X_1X_3;$$

The specified goal values for the properties as given in Table 8 were used to establish the goal function that was minimized to generate the following set of optimal parameters:

$$X_1 = 3.39$$
$$X_2 = 0 \text{ (wet granulation)} \qquad (19)$$
$$X_3 = 7.46$$

The associated experimental property values are given in Table 9.

O_1 (Y11)	O_2 (Y12)	O_3 (Y13)	O_4 (Y2)	O_5 (Y31)	O_6 (Y32)	O_7 (Y4)	O_8 (Y51)	O_9 (Y52)	O_{10} (Y6)
100.00	100.00	85.00	0.500	0.500	0.500	0.050	0.050	0.050	1.00

TABLE 8

Y11	Y12	Y13	Y2	Y31	Y32	Y4	Y51	Y52	Y6
97	104	106	0.49	0.58	0.73	0.031	0.008	0.047	<0.05%

TABLE 9

Applying the method for the particular case where only the minimum four ($n+1=3+1=4$) experimental runs required were used, runs 1, 3, 6 and 9 were selected to provide the parameter and property data as given in Table 7. As to the statistical analysis of parameters interaction, since a

correlation factor ρ_{13}=0.332 for the X_1X_3 interaction was calculated, that interaction cannot be considered as significant since 0.5 < ρ_{13} < 0.95 is not satisfied. The following property behavior relations were established:

$$\begin{aligned}
Y11 &= 85.36 + 0.99X_1 + 3.60X_2 - 0.34X_3;\\
Y12 &= 101.90 + 0.086X_1 + 2.30X_2 - 0.50X_3;\\
Y13 &= 102.87 + 0.38X_1 + 0.506X_2 - 0.58X_3;\\
Y2 &= 1.013 + 0.001X_1 - 0.019X_2 - 0.034X_3;\\
Y31 &= 0.88 - 0.038X_1 + 0.36X_2 + 0.0095X_3; \qquad (20)\\
Y32 &= 2.88 - 2.425X_1 + 14.33X_2 + 0.61X_3;\\
Y4 &= -0.02 - 0.080X_1 - 0.0007X_2 + 0.071X_3;\\
Y51 &= -0.\ 0568 - 0.065X_1 - 0.02X_2 + 0.06X_3;\\
Y52 &= -0.4 - 0.08X_1 + 0.55X_2 + 0.2X_3;\\
Y6 &= 2.84 + 0.68X_1 + 0.59X_2 - 0.1X_3.
\end{aligned}$$

The same specified goal values for the properties as given in Table 8 were used to establish the goal function that was minimized to generate the following set of optimal parameters:

$$\begin{aligned}
X_1 &= 3.32\\
X_2 &= 0 \text{ (wet granulation)} \qquad (21)\\
X_3 &= 7.09
\end{aligned}$$

The associated experimental property values are given in Table 10.

Y11	Y12	Y13	Y2	Y31	Y32	Y4	Y51	Y52	Y6
78	103	106	0.51	0.55	0.73	0.034	0.04	0.029	<0.05%

TABLE 10

Comparing the set of parameter values given at (20) with the former set obtained from all nine (9) experimental runs given at (19), it can be noted that both sets are very similar. Actually, from a pharmaceutical standpoint, they could almost be considered as identical.

CLAIMS:

1. A method of optimizing parameter values in a process of producing a product, said process being essentially controlled by a set of n parameters X_i affecting a set of k properties Y_j characterizing the product, said method comprising the steps of:

i) assigning values to a set of k property weights w_j representing relative importance of said properties Y_j for the characterization of said product;

ii) establishing property behavior mathematical relations giving an estimated property Ye_j for each said property Y_j in terms of said parameters X_i from given parameter data and associated property data;

iii) using said property weights w_j to establish a goal function in terms of property weighted deviations between the estimated properties Ye_j and corresponding specified goal values for said properties Y_j; and

iv) minimizing the goal function to generate a set of n optimal parameter values for said parameters X_i.

2. A method according to claim 1, wherein said product is a composition, said set of optimal parameter values characterizing an optimal formulation for the composition.

3. A method according to claim 1, wherein said product is a pharmaceutical product, said set of optimal parameter values characterizing an optimal formulation for the pharmaceutical product.

4. A method according to claim 1, 2 or 3, wherein the values for said property weights w_j are obtained using an algorithm based on an analytic hierarchy process.

5. A method according to claim 4, wherein said given property data are obtained through a number l of experimental runs of said process using said given parameter data, each said run using a distinct set of values for said given parameter data.

6. A method according to claim 5, wherein $l \geq n+1$.

7. A method according to any one of claims 1 to 6, wherein said goal function is expressed as follows:

$$G(X_i,...X_n) = \sum_{j=1}^{k} w_j^2 (Ye_j - O_j)^2$$

wherein O_j are said specified goal values for said properties Y_j. A method according to claim 7, wherein said minimizing step is performed by successive iterations of:

$$G(X_1,...,X_n) = \sum_{i=1}^{k} [f_i(X_1,...,X_n)]^2.$$

8. A method according to claim 7, wherein said goal function is minimized according to one or more specified ranges (a_i, b_i) wherein $a_i < X_i < b_i$ for one or more of said optimal parameter values.

9. A method according to any one of claims 1 to 8, further comprising the steps of:

i) performing experimentally said process using said set of optimal parameters values to obtain corresponding experimental values for said properties Y_j;

ii) ranking said set of optimal parameters values over predetermined alternative sets of parameters values for said X_i.

10. A method according to claim 9, wherein said ranking step is performed using an algorithm based on an analytic hierarchy process.

11. A method according to claim 9 or 10, further including the step of:

i) incorporating said set of optimal parameters values and said corresponding experimental values for said properties Y_j respectively into said given parameter and associated property data;

ii) repeating said steps ii) to iv) to generate a new set of optimal parameters values for said parameters X_i.

12. A method according to any one of claims 1 to 11, wherein said product is a pharmaceutical product.

13. A method according to any one of claims 1 to 11, wherein said product is a product.

14. A method according to claim 13, wherein said step of calculating comprises:

i) establishing property behavior mathematical relations giving an estimated property Ye_j for each said property Y_j in terms of said parameters X_i from said parameter data and associated property data;

ii) using said property weights w_j to establish a process goal function in terms of property weighted deviations between the estimated properties Ye_j and corresponding specified goal values for said properties Y_j; and

iii) minimizing the process goal function to generate a set of optimal parameter values for said parameters X_i.

15. A method according to claim 14, wherein the values for said property weights w_j are obtained by an algorithm based on an analytic hierarchy process.

16. A method according to claim 13, 14 or 15, wherein $l = n + 1$.

17. A method according to any one of claims 14 to 16, wherein said goal function is expressed as follows:

$$G(X_i,...X_n) = \sum_{j=1}^{k} w_j^2 (Ye_j - O_j)^2$$

wherein O_j are said specified goal values for said properties Y_j.

18. A method according to claim 17, wherein said minimizing step is performed through successive iterations.

19. A method according to claim 18, wherein said goal function is minimized according to one or more specified ranges (a_i,b_i) wherein $a_i < X_i < b_i$ for one or more of said optimal parameters values.

20. A method according to claim 14, further comprising the steps of:
performing experimentally said process using said set of optimal parameters values to obtain corresponding experimental values for said properties Y_j;
ranking said set of optimal parameters values over predetermined alternative sets of parameters values for said X_i.

21. A method according to claim 20, wherein said ranking step is performed through an algorithm based on an analytic hierarchy process.

22. A method according to claim 21, further including the steps of: incorporating said set of optimal parameters values and said corresponding experimental values for said properties Y_j respectively into said given parameter and associated property data;
repeating said steps a), b) and d) to generate a new set of optimal parameters values for said parameters X_i.

23. A method according to any one of claims 13 to 22, wherein said product is a pharmaceutical product.

24. A computer program product performing the method according to any one of claims 1 to 23.

Figure 1

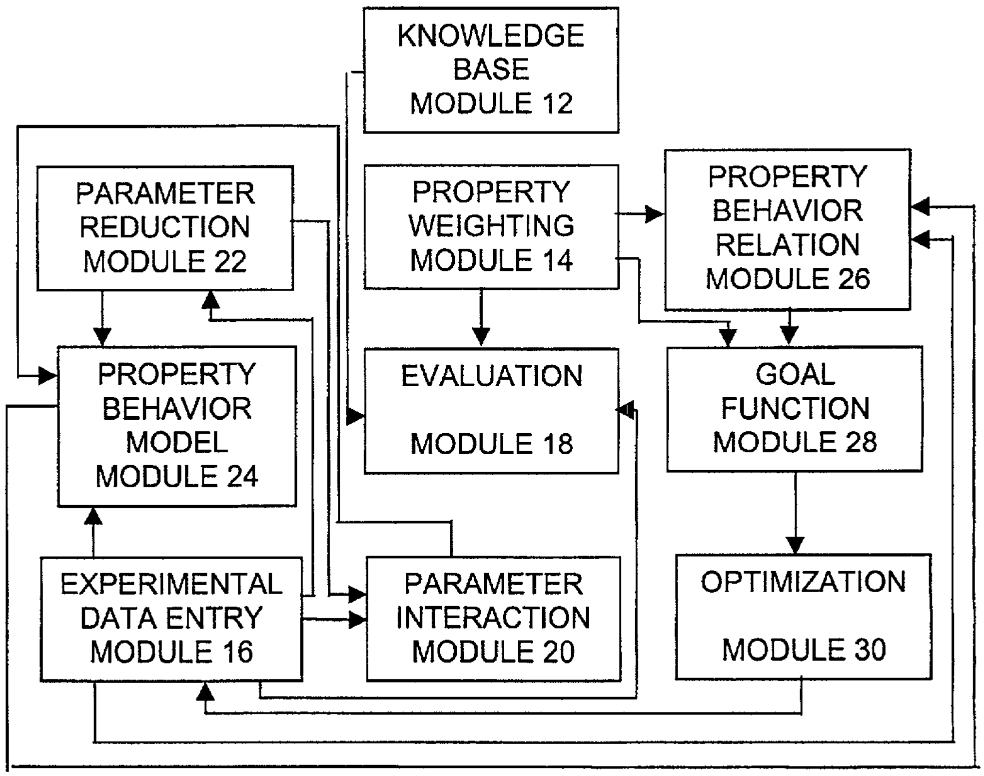
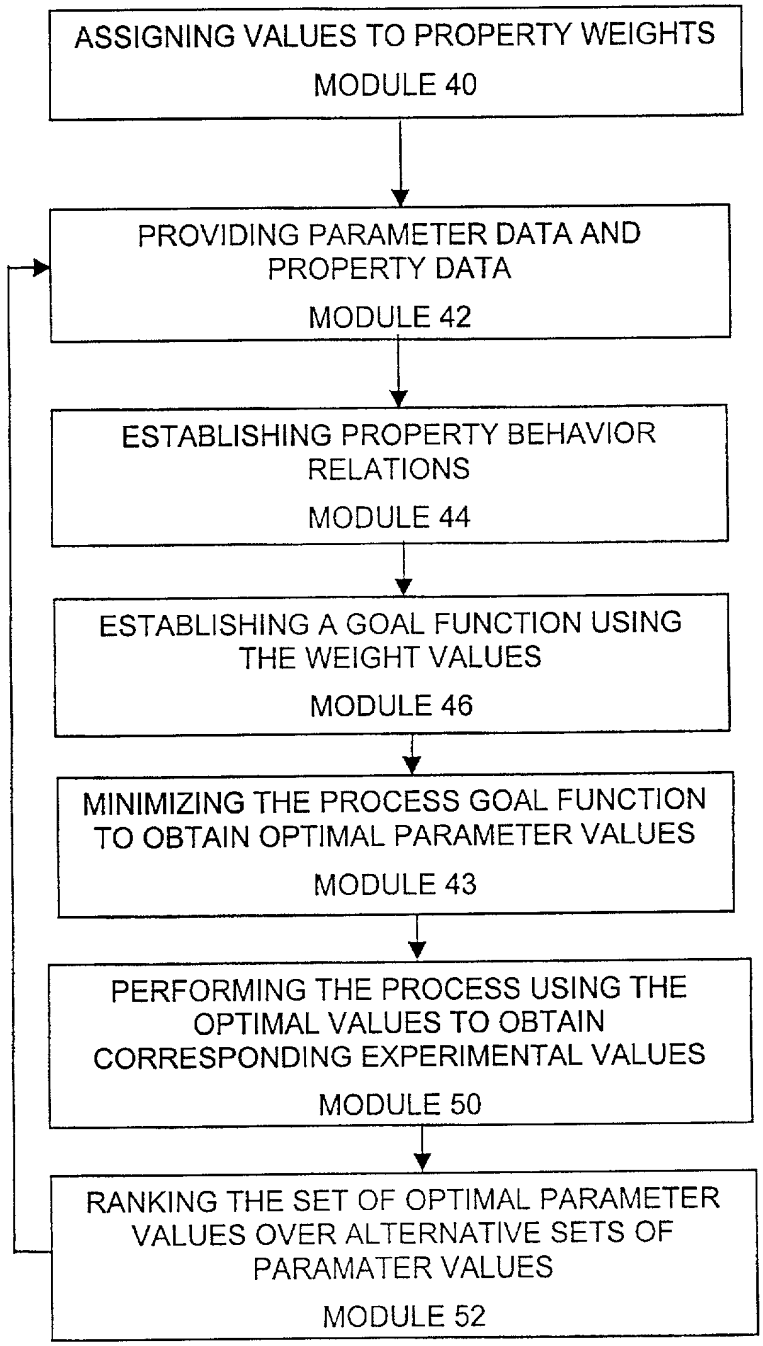

KNOWLEDGE BASE MODULE 12
PARAMETER REDUCTION MODULE 22
PROPERTY WEIGHTING MODULE 14
PROPERTY BEHAVIOR RELATION MODULE 26
PROPERTY BEHAVIOR MODEL MODULE 24
EVALUATION MODULE 18
GOAL FUNCTION MODULE 28
EXPERIMENTAL DATA ENTRY MODULE 16
PARAMETER INTERACTION MODULE 20
OPTIMIZATION MODULE 30

Figure 2


ASSIGNING VALUES TO PROPERTY WEIGHTS
MODULE 40
PROVIDING PARAMETER DATA AND PROPERTY DATA
MODULE 42
ESTABLISHING PROPERTY BEHAVIOR RELATIONS
MODULE 44
ESTABLISHING A GOAL FUNCTION USING THE WEIGHT VALUES
MODULE 46
MINIMIZING THE PROCESS GOAL FUNCTION TO OBTAIN OPTIMAL PARAMETER VALUES
MODULE 43
PERFORMING THE PROCESS USING THE OPTIMAL VALUES TO OBTAIN CORRESPONDING EXPERIMENTAL VALUES
MODULE 50
RANKING THE SET OF OPTIMAL PARAMETER VALUES OVER ALTERNATIVE SETS OF PARAMATER VALUES
MODULE 52

Declaration and Power of Attorney for Patent Application

Déclaration et Pouvoir pour Demande de Brevet

French Language Declaration

En tant qu'inventeur ci-après désigné, je déclare par la présente que:

Mon domicile, mon adresse postale et ma nationalité sont tels que figurant ci-dessous à côté de mon nom.

Je crois être le premier inventeur original et unique (si un seul nom est mentionné ci-dessous), ou l'un des premiers co-inventeurs originaux (si plusieurs noms sont mentionnés ci-dessous) de l'objet revendiqué, pour lequel une demande de brevet a été déposée concernant l'invention intitulée

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

" METHOD OF OPTIMIZING PARAMETER VALUES IN A PROCESS OF PRODUCING A PRODUCT "

et dont le mémoire descriptif est ci-joint à moins que la case suivante n'ait été cochée:

☒ a été déposée le 28 août 2000 sous le numéro de demande des États-Unis ou le numéro de demande internationale PCT PCT/CA00/00998 et modifiée par l'amendement préliminaire en date du 19 novembre 2001 accompagnant ce dépôt

Je déclare par la présente avoir révisé et compris le contenu du mémoire descriptif ci-dessus mentionné, incluant les revendications, telles que modifiées par toute modification ci-dessus mentionnée.

Je reconnais devoir divulguer toute information pertinente à la brevetabilité, tel que défini dans le Titre 37, §1.56 du Code fédéral des réglementations.

Je revendique par la présente la priorité étrangère, en vertu du Titre 35, §119(a)-(d) ou §365(b) du Code des États-Unis, sur toute demande étrangère de brevet ou certificat d'inventeur ou, en vertu du Titre 35, §365(a) du même Code, sur toute demande internationale PCT désignant au moins un pays autre que les États-Unis et figurant ci-dessous et, en cochant la case, j'ai aussi indiqué ci-dessous toute demande étrangère de brevet, tout certificat d'inventeur ou toute demande internationale PCT

the specification of which is attached hereto unless the following box is checked:

☒ was filed on August 28, 2000 as United States Application Number or PCT International Application Number PCT/CA00/00998 and was amended by the preliminary amendment dated November 19, 2001 filed herewith (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations., §1.56.

I hereby claim foreign priority under Title 35, United States Code, §119(a)-(d) or §365 (b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT International application which designated at least one country other than the United States, listed below, and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application

French Language Declaration

ayant une date de dépôt précédant celle de la demande à propos de laquelle une priorité est revendiquée.

on which priority is claimed.

Prior foreign application(s)
Demande(s) de brevet antérieure(s)

Priority Not Claimed
Droit de priorité non revendiqué

(Number) (Numéro)	(Country) (Pays)	(Day/Month/Year Filed) (Jour/Mois/Année de dépôt)	☐
(Number) (Numéro)	(Country) (Pays)	(Day/Month/Year Filed) (Jour/Mois/Année de dépôt)	☐

Je revendique par la présente tout bénéfice, en vertu du Titre 35, §119(e) du Code des États-Unis, de toute demande de brevet provisoire effectuée aux États-Unis et figurant ci-dessous.

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.

60/152,457 (Application No./ N° de demande)	September 3, 1999 (Filing Date/ Date de dépôt)
(Application No./ N° de demande)	(Filing Date/ Date de dépôt)

Je revendique par la présente tout bénéfice, en vertu du Titre 35, §120 du Code des États-Unis, de toute demande de brevet effectuée aux États-Unis, ou en vertu du Titre 35, §365(c) du même Code, de toute demande internationale PCT désignant les États-Unis et figurant ci-dessous et, dans la mesure où l'objet de chacune des revendications de cette demande de brevet n'est pas divulgué dans la demande antérieure américaine ou internationale PCT, en vertu des dispositions du premier paragraphe du Titre 35, §112 du Code des États-Unis, je reconnais devoir divulguer toute information pertinente à la brevetabilité, tel que défini dans le Titre 37, §1.56 du Code fédéral des réglementations, dont j'ai pu disposer entre la date de dépôt de la demande antérieure et la date de dépôt de la demande nationale ou internationale PCT de la présente demande:

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s), or §365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

(Application No.) (N° de demande)	(Filing Date) (Date de dépôt)	(Status) (patented, pending, abandoned) (Statut) (breveté, en cours d'examen, abandonné)
(Application No.) (N° de demande)	(Filing Date) (Date de dépôt)	(Status) (patented, pending, abandoned) (Statut) (breveté, en cours d'examen, abandonné)

French Language Declaration

Je déclare que toute les déclarations faites dans la présente sont à ma connaissance, véridiques et que toutes les déclarations faites à partir de renseignements ou de suppositions sont tenues pour véridiques; et de plus, que toutes ces déclarations ont été faites en sachant que toute fausse déclaration volontaire ou son équivalent est passible d'une amende ou d'une peine d'emprisonnement, ou des deux, en vertu de la Section 1001 du Titre 18 du Code des États-Unis, et que de telles déclarations volontairement fausses risquent de compromettre la validité de la demande de brevet ou du brevet délivré à partir de celle-ci.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POUVOIR: En tant qu'inventeur désigné, Je nomme par la présente l'(les) avocat(s) et/ou agent(s) inclus sous le numéro de client officiel suivant, avec plein pouvoir de révocation et de substitution, chargés de poursuivre cette demande et de traiter toute affaire s'y rapportant avec l'Office des brevets et des marques: *(mentionner le nom et le numéro d'enregistrement).*

POWER OF ATTORNEY: As a named inventor, I hereby appoint the agents and/or attorneys included in the following Customer Number, with full power of substitution, association, and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: *(list name and registration number)*

Please send all correspondence and direct all telephone calls to: / Veuillez adresser toute correspondance et tout appel téléphonique à:

020988

PATENT AND TRADEMARK OFFICE

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Full name of second inventor (Nom complet du second co-inventeur)	Citizenship (Nationalité)	Date (dd/mm/yyyy) (jj/mm/aaaa)
Residence and Post Office address (Domicile et adresse postale)	Second Inventor's signature (signature du second inventeur)	
Full name of third co-inventor (Nom complet du troisième co-inventeur)	Citizenship (Nationalité)	Date (dd/mm/yyyy) (jj/mm/aaaa)
Residence and Post Office address (Domicile et adresse postale)	Third Inventor's signature (signature du troisième inventeur)	
Full name of fourth co-inventor (Nom complet du quatrième co-inventeur)	Citizenship (Nationalité)	Date (dd/mm/yyyy) (jj/mm/aaaa)
Residence and Post Office address (Domicile et adresse postale)	Fourth Inventor's signature (Signature du quatrième inventeur)	